I’m a physiologist, so I have no excuse. I know that exercise is good for me, but all too often I neglect physical activity for other pursuits, sitting at my desk for hours working on my computer. I know to get up and move around, to become more active. Sound familiar? Like so many of us, my priorities are wrong, so I write editorials to remind myself. But we have been reminded over and over again and should all remember that “it is health that is real wealth and not pieces of gold and silver” (Mahatma Gandhi). Physiology provides us with the insight necessary for health and well-being—we should pay more attention! In this issue of Physiology, we explore the link between physiology and all aspects of health. The very first article should be convincing in this respect, showing the link between physical activity, cognition, and mental health, with the take home message: “go run; it clears the mind.”

We all know that exercise is beneficial for our general health (e.g., prevention of hypertension, heart disease, Type 2 diabetes, metabolic syndrome, osteoporosis, and metastatic diseases), but what is less appreciated is the beneficial effect of physical activity for brain function. Studies in rodents and humans indicate that exercise improves cognition and mood, might delay or prevent age-related memory decline, and can aid recovery from brain damage caused by injury or disease. Rodent studies have led to insight into the underlying mechanisms. Voluntary wheel running increases the production of new neurons (neurogenesis), neurotrophins, neurotransmitters, and angiogenesis in the hippocampus, a brain area important for learning and memory. In addition, running alters the development and function of new neuronal circuitry. In their review (4), Vivar and van Praag describe their studies showing that changes in the hippocampal neuronal network occur after only 1 wk of voluntary wheel running in young adult male mice. They found that this neural plasticity is mainly attributable to modifications in glutamatergic neurotransmission onto newly born hippocampal neurons. They also show that longer periods of wheel-running activity (1 mo or more) increase input to new hippocampal neurons from multiple brain areas important for learning and memory (entorhinal cortex, septum, and mammillary nuclei). Interestingly, these same brain areas are also considered to be vulnerable in normal aging and neurodegenerative diseases.

For decades, it has been known that skeletal muscles express large amounts of membrane ClC-1 chloride channels. Based on studies showing that loss of ClC-1 chloride channels leads to hyperexcitability and ensuing myotonia with spontaneous muscle activation, the general accepted concept was that the role of ClC-1 channels was to provide large resting conductance for Cl−, thereby reducing skeletal muscle fiber excitability to levels where there is no generation of spontaneous action potentials. However, detailed analysis of the importance of the resting membrane Cl− conductance suggests that conductance can be substantially reduced before muscles become myotonic. In their review (2), Nielsen and colleagues take this a step further by demonstrating that the opening of the ClC-1 channels is highly regulated in working skeletal muscles and that this does not cause myotonia but rather serves to maintain muscle excitability and, thus, function. Thus, in their review, the authors suggest a completely new physiological role for the ClC-1 channels in muscle. In this concept, a downregulation of the ClC-1 channel opening in active muscles provides an explanation for why active but not resting muscles can tolerate large elevations in extracellular K+ that can take place during strenuous exercise. It also explains why accumulation of lactic acid under some circumstances may be protective against fatigue instead of causing fatigue. Obtaining a better understanding of fatigue mechanisms is relevant for many work and exercise scenarios but may also be particularly important to understand and treat the reduction in muscle function that occurs in association with many neuromuscular diseases.

The conventional view of sodium-glucose-linked transporter (SGLT) proteins is that they are very important in the intestinal absorption of sugar from the diet and prevention of glucose loss in the urine. Such a functional role is apparent from SGLT mutations that cause glucose and galactose malabsorption and glucosuria. In their review (5), Wright and colleagues discuss recent studies that have uncovered a variety of unexpected functions for these transport proteins. SGLTs are members of a gene family that include a protein responsible for iodide accumulation in the thyroid gland, and are members of a structural family of proteins that include those responsible for the accumulation of neurotransmitters in the nervous system. There is evidence that these diverse transport proteins work by a very similar mechanism. SGLTs also behave as water transporters in the gut and glucose sensors throughout the body. Surprisingly, SGLT inhibitors provide an approved new therapy to treat Type 2 diabetes. SGLTs are expressed in pancreatic, prostate, and brain cancers, and there is preliminary evidence that SGLT inhibitors may be used to treat cancer. Recent studies demonstrate that SGLT1 is expressed in activated T-lymphocytes and that it plays an important role in the defense against infection. Finally, there is emerging evidence that SGLT1 in uterine tissue is important in maintaining normal fetal growth and development, and that SGLT1 deficiency in women may predispose them to early pregnancy failure. Further research is needed to answer the many unresolved problems in the field of SGLT biology and to contribute to new therapies for a wide variety of diseases.

The mammalian vascular system consists of two closely associated and functionally specialized networks: the circulatory and the lymphatic vasculature. Both vasculatures are highly branched and lined by endothelial cells. The lymphatic vasculature is important for fluid homeostasis, immune surveillance, and lipid absorption. It is also the main route for metastatic cells to...
spread in the body, and inflammation-de-
fective lymphatics can lead to lymphedema
and other associated disorders. In their re-
view (1), Ma and Oliver discuss newly dis-
covered functional roles for the lymphatic
vasculature in cardiovascular disease, glau-
coma, cholesterol and salt regulation, me-
tabolism, obesity, and neurological
disorders. Importantly, it also has been
shown that lymphatic endothelial cells
(LECs) remain plastic throughout life and
that their fate is reprogrammable. LEC fate
manipulation could lead to therapies
for a variety of pathological conditions,
such as inflammation, tumorigenesis,
and tissue injury. However, the extent
and precise role of LEC plasticity remains
to be defined before novel, cell-based
therapies for vascular diseases can be
developed.

Lactic acid is no longer regarded as
merely a dead-end product of glycolysis.
It has become clear that lactic acid is a
signaling molecule and a powerful reg-
ulator in multiple conditions of health
and disease, including energy regula-
tion, immune modulation, memory for-
tation, wound repair, ischemic tissue
injury, and cancer progression. In their
review (3), Sun and colleagues discuss
lactic acid transport, signaling, and
functions in several pathophysiological
processes. Although lactate administra-
tion to wounds likely promotes healing,
in cancer it enhances metastasis. As
such, it is a double-edged sword, with
the potential to work for or against
health. Although advances have been
significant, further research and a better
understanding of the functions and reg-
ulations of lactic acid can elucidate
ways to exploit its influences and bene-
fit patient care.

No conflicts of interest, financial or otherwise,
are declared by the author.

References
1. Ma W, Oliver G. Lymphatic endothelial cell plas-
ticity in development and disease. Physiology
(Bethesda) 32: 444–452, 2017. doi:10.1152/
2. Nielsen OB, Riisager A, de Paoli FV, Pedersen
TH. Chloride channels take center stage in acute
regulation of excitability in skeletal muscle: im-
plications for fatigue. Physiology (Bethesda) 32:
3. Sun S, Li H, Chen J, Qian Q. Lactic acid: no longer
an inert and end-product of glycolysis. Physiol-
ogy (Bethesda) 32: 453–463, 2017. doi:10.1152/
4. Vivar C, van Praag H. Running changes the brain:
the long and the short of it. Physiology (Be-
5. Wright EM, Ghezzi C, Loo DDF. Novel and unex-
pected functions of SGLTs. Physiology (Be-